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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/666,884	09/19/2003	Anwer Basha	7128US01	6816

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EXAMINER	
HUANG, EVELYN MEI	
ART UNIT	**PAPER NUMBER**
1625	

DATE MAILED: 05/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/666,884	BASHA ET AL.	
	Examiner	Art Unit	
	Evelyn Huang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-28* is/are pending in the application.

4a) Of the above claim(s) *10-18 and 24-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9 and 19-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-28 are pending.

Election/Restrictions

2. Certain errors occur in the restriction requirement mailed on 12-23-2004. A correction is hereby made. The claims and descriptions in the first three groups of the restriction requirement should be as follows:

I. Claims 1-9, 22-23 in part drawn to a compound wherein Z is a 3, ***8*** diazabicyclo[3.2.1]octane, classified in class 544, subclass 349, and the composition thereof. If this group were elected, election of a species within the elected invention would be required.

II. Claims 19, 20 and claim 1-9, 21-23 in part, drawn to a compound wherein Z is a 3, ***6***- diazabicyclo[3.2.1]octane or 3, 8 -diazabicyclo[4.2.0]octane , classified in class 546, subclass 113, and the composition thereof. If this group were elected, election of a species within the elected invention would be required.

III Claims 10-18, and claims ***1-7***, 21-23 in part, drawn to a compound wherein Z is a diazabicyclo[3.2.0]heptane or an octahydro- pyrrolo[3,4c]pyrrole, classified in class 548, subclass 453, and the composition thereof. If this group were elected, election of a species within the elected invention would be required.

In response to the restriction requirement mailed on 12-23-2004, Applicant has selected without traverse the invention of Group II, claims 19, 20 and claims 1-9, 21-23 in part. The species elected is Example 6. However, Example 6 does not fall within the elected Group II. Claims of Group I, III-VI are withdrawn from further consideration as being drawn to the non-elected inventions.

Claim Rejections - 35 USC § 112(2)

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-9, 19-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claim 1, what are the substituents on the heteroaryl, bicyclic heteroaryl and phenyl? The substituents should be positively recited in the claim to provide antecedent basis for the claims dependent thereon.

b. Claim 5, the substituents on phenyl have no antecedent basis in the base claim 1. Furthermore, the definitions for R_AR_B are missing in the claims.

c. Claim 6, R4 has no antecedent basis in the base claim 1. Furthermore, the definitions for R_AR_B are missing in the claims.

d. Claim 20, alkylcarbonyl as a substituent on phenyl has no antecedent basis in the base claim 19, which is dependent on claim 1.

e. Claim 9, the substituents on phenyl have no antecedent basis in the base claim 8, which is dependent on claim 1. Furthermore, the definitions for R_AR_B are missing in the claims.

The rejection is applicable to claims dependent on the above claims.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 19-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making the compounds of claims 9, 20, 22, and the pharmaceutical salts thereof, does not reasonably provide enablement for making the prodrugs of these compound or the other compounds in the generic claims and the prodrugs thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

a. *Nature of the invention.*

The instant invention is drawn to a substituted diazabicycloalkane compound of formula I and the pharmaceutically acceptable ester, amide or prodrugs thereof.

b. *State of the prior art and the level of the skill in the art.*

It is well known in the art that for a compound to be a prodrug, it has to be biologically inactive, but it has to be metabolized to the active substance under the physiological conditions at a concentration effective for therapeutic use (Wolff ME. 'Burger's Medicinal Chemistry and Drug Discovery'. Fifth Edition. John Wiley & Sons. 1995, pages 975-977). Extensive development is required to find the correct chemical modification for a specific drug. Once a prodrug is formed, it is a new drug entity and requires extensive and costly studies to determine safety and efficacy (Banker et al. 'Modern Pharmaceutics'. Third Edition. Marcel Dekker, New York, 1996, page 596, third paragraph)

The level of the skilled in the chemical synthetic art is high.

c. *Predictability/unpredictability of the art.*

The high degree of unpredictability is well recognized in the synthetic art. Predicting if a certain prodrug, such as an ester of a claimed alcohol, is in fact a prodrug that is metabolized to a therapeutic concentration and at a useful rate is filled with experimental uncertainty.

Furthermore, it is difficult to extrapolate results from animal models to humans, since not only metabolism of the active moiety might differ, but also its availability from the prodrug (Wolff, page 976, Section 10, second paragraph).

d. *Amount of guidance/working examples.*

Preparation of example compounds is limited to those wherein Ar1 is pyridazinyl, and Ar2 is optionally substituted phenyl. An example of the prodrug, an ester or amide of the inventive compound of formula I is not found in the specification.

Starting material and the process of making the instantly claimed compounds other than the example compounds, are not seen but required. Sources are particularly pertinent because absent sources, the public is offered mere language, rather than enablement. Ex parte Moersch 104 USPQ 122. In re Howarthe 210 USPQ 689.

e. *The breadth of the claims.*

The claims as recited embrace diverse groups of compounds, some structurally removed from the example compounds (especially those wherein Ar2 is any bicyclic heteroaryl further substituted with multiple substitutents), as well as the potential prodrug derivatives thereof, (which includes the as yet unidentified classes of prodrugs). The scope of the claims therefore does not commensurate with the scope of the objective enablement, especially in view of the high degree of unpredictability in the art and the absence of working examples (paragraphs b, c, d above).

f. *Quantitation of undue experimentation.*

Since sufficient teaching and guidance have been provided in the disclosure, one of ordinary skill in the art (paragraphs b-e above), even with high degree of skill, would not be able to make and use all the compounds and the prodrugs thereof as claimed without undue experimentation.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-4, 21, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schrimf (WO 2001081347, published on 11-01-2001, PTO-1449, or its equivalent, US 20020019388. published on 2-14-2002, PTO-1449, both are available as prior art under 102(b)). The following reference is made to the US publication, but is applicable to the WO patent.

Schrimf generically discloses a diazabicylic CNS active compound which encompasses the instant (page 72, claims 1-3, 13, 14). The composition thereof is also described and claimed (page 78, claim 71). Specific examples, such as 3-pyridinyl-3,8-diazabicyclo-[4.2.0]octane, are described (page 74, claim 15).

Schrimf's 3-pyridinyl-3,8-diazabicyclo[4.2.0]octane (claim 15, first compound) has a hydrogen on the pyridinyl, whereas the instant has a 5-membered heteroaryl, such as tetrazolyl on the pyridinyl.

Schrimf, however, teaches that hydrogen and tetrazolyl are optional choices on the pyridinyl (pages 72-3, claim 1, definition of R5).

At the time of the invention, one of ordinary skill in the art would be motivated to replace the hydrogen with the alternative tetrazolyl on the pyridinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional CNS active compound, since Schrimf had clearly taught that any species within the disclosed genus would be useful for selectively controlling neurotransmitter release.

7. Claims 1-4, 21, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunnelle (2003/0225268, which is available as prior art under 102(e)).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter

disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Brunelle generically discloses a diazabicylic compound useful for controlling synaptic transmission (pages 38-39, claim 1; page 46, claims 35, 36). The composition thereof is also described and claimed (page 48, claim 44). Specific examples, such as 3-pyridinyl-3,6-diazabicyclo-[3.2.1]octane, are described and claimed (pages 46-47, claim 37).

Brunelle's 3-pyridinyl-3,6-diazabicyclo[3.2.1]octane (page 47, claim 37, last compound) has a hydrogen on the pyridinyl, whereas the instant has a 5-membered heteroaryl, such as tetrazolyl on the pyridinyl.

Brunelle, however, teaches that hydrogen and tetrazolyl are optional choices on the pyridinyl (pages 38-39, claim 1, definition of R6).

At the time of the invention, one of ordinary skill in the art would be motivated to replace the hydrogen with the alternative tetrazolyl on the pyridinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional CNS active compound, since Brunelle had clearly taught that any species within the disclosed genus would be useful for controlling synaptic transmission.

8. Claims 1-4, 21, 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bunnelle (WO 00/44755, which is available as prior art under 102(b)).

Brunelle generically discloses a diazabicylic compound useful for controlling synaptic transmission (pages 98-99, claim 1; page 114, claims 35, 36). The composition thereof is also described. Specific examples, such as 3-pyridinyl-3,6-diazabicyclo-[3.2.1]octane, are described and claimed (pages 114-5, claim 37).

Brunelle's -3-pyridinyl-3,6-diazabicyclo[3.2.1]octane (page 47, claim 37, last compound) has a hydrogen on the pyridinyl, whereas the instant has a 5-membered heteroaryl, such as tetrazolyl on the pyridinyl.

Brunelle, however, teaches that hydrogen and tetrazolyl are optional choices on the pyridinyl (pages 98-99, claim 1, definition of R6).

At the time of the invention, one of ordinary skill in the art would be motivated to replace the hydrogen with the alternative tetrazolyl on the pyridinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional CNS active compound, since Brunelle had clearly taught that any species within the disclosed genus would be useful for controlling synaptic transmission.

9. Claims 1-9, 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller (US 2002/0013309, PTO-1449, which is available as prior art under 102(b)).

Miller generically discloses a CNS active diazabicyclic compound (page 2). A specific example, 6-methyl-3-(5-phenyl-3-pyridyl)-3,6-diazabicyclo-[3.2.1]octane, is described (page 4, [0040]). See paragraph 10 below.

The species compound of instant claim 22 has a pyridazinyl instead of Miller's pyridinyl. However, pyridinyl and pyridazinyl are optional choices within a small genus (page 12, claim 1, definition of X, X', X").

At the time of the invention, one of ordinary skill in art would be motivated to replace the pyridinyl with the alternative pyridazinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional CNS active compound, since Miller had clearly taught that any species within the narrow disclosed genus would be effective for treating a CNS disorder.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 21, 23 are rejected under 35 U.S.C. 102(b) as being anticipated by Miller (US 2002/0013309, PTO-1449).

The CNS active compound, 6-methyl-3-(5-phenyl-3-pyridyl)-3,6-diazabicyclo-[3.2.1]octane (page 4, [0040]), and the pharmaceutical composition thereof, are encompassed by the instant wherein R 1 is methyl, Ar1 is pyridinyl, and Ar2 is phenyl.

Double Patenting

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

12. Claims 1-9, 19-23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7, 19-23 of copending Application No. 10/942035. Although the conflicting claims are not identical, they are not patentably distinct from each other. The copending compound embraces the instant. The 6-methyl 3-(6-phenyl-pyridazin-3-yl)-3,6-diazabicyclo[3.2.1]octane, 6-phenyl-pyridazin-3-yl-3,8-diazabicyclo[4.2.0]octane species of copending claim 23, and the composition thereof, are encompassed by the instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 1-4, 21, 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 13-15, 71 of copending Application No. 10/810999 (divisional of 09/833914, published as US 2002/0019388). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The 3-pyridinyl-3,8-diazabicyclo[4.2.0]octane of the copending claim 15 (first compound) has a hydrogen on the pyridinyl, whereas the instant has a 5-membered heteroaryl, such as tetrazolyl on the pyridinyl. However, halogen and tetrazolyl are optional choices on the pyridinyl (claim 1, definition of R5). At the time of the invention, one of ordinary skill in the art would be motivated to replace the chloro with the alternative tetrazolyl on the pyridinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional CNS active compound.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 1-4, 21, 23 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 35-37, 44 of copending Application No. 10/412510 (published as US 2003/0225268). Although the conflicting claims are not identical, they are not patentably distinct from each other.

The 3-pyridinyl-3,8-diazabicyclo[4.2.0]octane of the copending claim 37 has a hydrogen on the pyridinyl, whereas the instant has a 5-membered heteroaryl, such as tetrazolyl on the pyridinyl. However, hydrogen and tetrazolyl are optional choices on the pyridinyl (claim 1, definition of R6). At the time of the invention, one of ordinary skill in the art would be motivated to replace the hydrogen with the alternative tetrazolyl on the pyridinyl to arrive at the instant invention, with the reasonable expectation of obtaining an additional compound useful for controlling synaptic transmission.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Evelyn Huang whose telephone number is 571-272-0686. The examiner can normally be reached on Tuesday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Evelyn Huang
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Art Unit 1625